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(21) International Application Number: PCT/US94/08742 (22) International Filing Date: 3 August 1994 (03.08.94) (30) Priority Data: 08/101,724 4 August 1993 (04.08.93) US (71) Applicant: ANDRULIS PHARMACEUTICALS CORPORATION [US/US]; Suite 113, 11800 Baltimore Avenue, Beltsville, MD 20705 (US). (72) Inventor: ANDRULIS, Peter, J., Jr.; 7220 Armat Drive, Bethesda, MD 20817 (US). (74) Agent: REA, Teresa, Stanek; Burns, Doane, Swecker & Mathis, Washington and Prince Streets, P.O. Box 1404, Alexandria, VA 22313-1404 (US).			(81) Designated States: AU, CA, CN, JP, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>Without international search report and to be republished upon receipt of that report.</i>
(54) Title: TREATMENT OF RHEUMATOID ARTHRITIS WITH THALIDOMIDE ALONE OR IN COMBINATION WITH OTHER ANTI-INFLAMMATORY AGENTS			
(57) Abstract <p>The present invention relates to a novel method for treating rheumatoid arthritis with thalidomide alone or in combination with anti-rheumatoid agents and/or with steroidal and/or non-steroidal anti-inflammatory drugs. The present invention also relates to methods of treating rheumatoid arthritis with tumor necrosis factor inhibitors as well as pharmaceutical compositions containing tumor necrosis factor inhibitors and steroidal and/or non-steroidal anti-inflammatory and/or anti-rheumatoid drugs. A further aspect of this invention relates to a special pharmaceutical composition containing thalidomide wherein said thalidomide has been micronized to a particle size of less than 1.0 microns. Compositions containing such micronized thalidomide exhibit faster absorption rates than previously known thalidomide formulations.</p>			

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**TREATMENT OF RHEUMATOID ARTHRITIS WITH
THALIDOMIDE ALONE OR IN COMBINATION WITH
OTHER ANTI-INFLAMMATORY AGENTS**

5 The present invention relates to a novel method for treating rheumatoid
arthritis with thalidomide alone or in combination with anti-rheumatoid agents
and/or with steroidal and/or non-steroidal anti-inflammatory drugs. The present
invention also relates to methods of treating rheumatoid arthritis with tumor
necrosis factor inhibitors as well as pharmaceutical compositions containing
tumor necrosis factor inhibitors and steroidal and/or non-steroidal anti-
10 inflammatory and/or anti-rheumatoid drugs. A further aspect of this invention
relates to a special pharmaceutical composition containing thalidomide wherein
said thalidomide has been micronized to a particle size of less than 1.0 microns.
Compositions containing such micronized thalidomide exhibit faster absorption
rates than previously known thalidomide formulations.

15

DESCRIPTION OF THE PRIOR ART

Thalidomide was first synthesized and marketed in Germany in the 1950's
as a sedative. The toxicity of the compound was so low that a dose killing 50%
of animals (LD₅₀) could not be established. Thalidomide therefore, promised to
be a safer alternative to the use of Barbiturates. In 1961 Thalidomide was
20 realized to be responsible for an epidemic of malformations. The incidence of
malformed babies paralleled the sales of thalidomide preparations and dropped to
the extremely low values of the pre-thalidomide era after the drug was withdrawn
from the market.

Oral administration of thalidomide in the range of 100 to 200mg in
25 humans results in maximal blood concentration of 0.9 to 1.5mg/L after 4 to 6h.
The hydrolytic cleavage in serum is much slower than *in vitro* at pH 7.4. This
may be because thalidomide is highly bound to plasma proteins. Studies and
experimental animals showed high concentrations of the drug in the
gastrointestinal tract, liver and kidney, and lower concentrations in muscle, brain

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and adipose tissue. In pregnant animals, thalidomide is able to pass across the placental barrier.

Although total studies of thalidomide metabolism in humans do not exist, in animals the main pathway of degradation appears to be nonenzymatic hydrolytic cleavage. The biochemical mechanism of non-sedative effects of thalidomide is unclear. Very little work has been done to understand the immunomodulatory effect of the compound on a molecular basis.

The current therapeutic uses of thalidomide include the following: acute and Chronic Graft-Versus-Host-Disease, Aphthosis, Cold hemagglutinin disease, Colitis, Cutaneous lupus erythematosus, Erythema nodosum leprosum, Erythema multiform, Histiocytosis, Immune complex vasculitis, Jessner-Kanof's disease, Lichen planus, Pemphigoid disorders, Photodermatoses, Prurigo nodularis, Pyoderma gangraenosum, Rheumatoid arthritis, Sarcoidosis, and Weber-Christian's disease as well as HIV *in vitro*.

Rheumatoid arthritis is a chronic, progressive, inflammatory arthritis involving multiple joints, characterized by a tendency to spontaneous remissions and subsequent relapses. Within the context of the present application, rheumatoid arthritis (RA) is defined to also include juvenile rheumatoid arthritis. Rheumatoid arthritis has many manifestations which affect different parts of the body. One simple definition is that rheumatoid arthritis is a disease of articular joints in which the cartilage and bone is slowly eroded away by a proliferative, invasive connective tissue called panus, which is derived from the synovial membrane and may involve peri-articular structures such as bursae, tendon sheets, and tendons as well as extra-articular tissues such as the subcutaneous, cardiovascular system, lungs, spleen, lymph nodes, skeletal muscles, central and peripheral nervous systems, and the eyes. Typical symptoms which are indications of a poor prognosis are subcutaneous nodules, vasculitis, neuritis, cardiopulmonary disease, pericarditis, Sjogren's syndrome, and Feltys syndrome. Ancillary abnormalities of the disease include anemia, elevated erythrocytes sedimentation rate (ESR), high titer serum rheumatoid factor (RF), and

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inflammatory synovial fluid. Affected bone is demineralized, eroded, and then deformed. The origin of rheumatoid arthritis is as yet not fully understood.

Recent studies suggest involvement of both humoral and cell-mediated immune responses in the underlying chronic inflammatory reaction occurring in the joint. Tumor necrosis factor has been also implicated in rheumatoid arthritis disease. Rheumatoid factor is the most widely recognized serum marker in rheumatoid arthritis. In one scenario, a virus, a small bacterium, or some other agent induces an inflammatory defense response that persists in some patients. By-products of the immune reaction inflame the synovium and trigger the destructive joint changes which cause pain, stiffness, functional impairment and fatigue in patients.

Evidence of the proximal molecular and or cellular cause of rheumatoid arthritis and, therefore, prospective targets of thalidomide action is diverse. Myachi found that thalidomide decreased generation of superoxide and hydroxide radicals in the synovial fluid of rheumatoid arthritis patients. He proposed that thalidomide may act by reducing these polymorphonuclear leukocyte generated oxygen radical intermediates which are significantly increasing in the synovial fluids.

Iwakura reports evidence that implicates HTLV-1 as an etiological agent in the development of rheumatoid arthritis. Marrack reports that V β 14+ T-cells were prevalent in the synovial fluid of rheumatoid arthritis patients and implicates them in the etiology of rheumatoid arthritis.

Sigler has identified high concentrations of the enzyme phospholipase A₂ (PLA₂) in the synovial fluid of patients with rheumatoid arthritis. PLA₂ is secreted in response to tumor necrosis factor; its hydrolysis of phosphoglycerides to release arachidonate is the rate determining step in the production of eicosanoid mediators of inflammation. Therefore, tumor necrosis factor and/or PLA₂ may play key roles in inflammation and the ability of thalidomide to prevent production or action of tumor necrosis factor may inhibit the phosphoglyceride-arachidonate-eicosanoid inflammatory cascade.

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To date, the different treatments of rheumatoid arthritis have proved unsatisfactory. Traditionally, non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin and aspirin-like drugs are used for the symptomatic treatment of RA in humans. Steroids have also been used. However, while steroids provide symptomatic relief, they do not prevent destruction caused by arthritis. Steroids can also lead to diabetes, cataracts, and increased rate of infections.

5 Additionally, there is often a rapid reappearance of the active disease when treatment is ended. On the other hand, clinicians over the years have used a number of drugs which they argue reduces the rapid progression of rheumatoid arthritis. These drugs are termed "fundamental" or "disease-modifying drugs", or "disease-modifying anti-rheumatic drugs." These drugs include for example; gold salts; metal chelators such as D-penicillamine; antimalarial drugs such as chloroquine, dapsone, and sulfasalazine.

15 Cytotoxic and immunosuppressive drugs have also been used to control rheumatoid arthritis. Methotrexate and cyclophosphate are both immunosuppressive and cytotoxic. The immunosuppressive drugs include cyclosporin and corticosteroids.

Gutierrez-Rodriguez reports that use of 400 to 600mg per day of thalidomide for 7 to 20 weeks in seven patients, in some cases in conjunction with aspirin or prednisone, causes decrease, normalization or elimination of pain, a decrease in erythrocyte sedimentation rate (ESR), and rheumatoid factor (RF) titers in some or all patients. In a later report Gutierrez-Rodriguez reports that of 15 patients receiving thalidomide at a dosage of 400 to 600mg per day for 7 to 38 weeks (in two patients 300mg per day 62 and 65 weeks), seven achieved complete remission with disappearance of pain, inflammation, joints stiffness and abnormal ESR. Five achieved partial remission and three showed no improvement. Of five relapses, all reattained remission, three of four for nine to twenty-four months on induction therapy and 2 for 30 to 36 months on induction therapy followed by maintenance therapy of 100mg per day. All told, pain disappeared in 12 of 15 patients; RF became negative in 3 of 4 cases, decreased

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in 10 of 14, showed no change in 1 of 14; ESR became normal in 7 of 15 and markedly decreased in 8 of 15 and the articular index (AI) reached zero in 10 of 15 and sharply decreased in 5 of 15 patients.

SUMMARY OF THE INVENTION

5 The primary object of the present invention is to provide a method for the treatment of rheumatoid arthritis with tumor necrosis factor inhibitors.

A further object of the present invention is the treatment of rheumatoid arthritis with thalidomide, alone and in combination with steroidal anti-inflammatory agents and/or nonsteroidal anti-inflammatory agents and/or anti-rheumatoid agents.

10 Another object of the present invention is to provide a method for treating rheumatoid arthritis with thalidomide at a given regimen.

An additional object of the present invention is to provide compositions of matter comprising tumor necrosis factor inhibitors with non-steroidal anti-inflammatory drugs and/or steroidal anti-inflammatory drugs and/or antirheumatic drugs.

15 Still another object of the present invention is to provide a composition of matter containing thalidomide having a specific particle size.

A further object of the present invention is to provide a thalidomide or tumor necrosis factor inhibitor mediated therapy in which dosages of other drugs can be substantially reduced.

20 A still further object of the present invention is a method for the therapeutic treatment of rheumatoid arthritis which comprises treatment with thalidomide and other drugs on alternate days (by diverse schedules).

25 DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention deals with a treatment of rheumatoid disorders which comprises administering to a patient in need of such treatment, a daily dosage form during an uninterrupted consecutive sequence of 365 days, and in

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accordance with the following regimen: (a) a three time a day, oral dose in an uninterrupted consecutive sequence of not more than 365 days of a tumor necrosis factor inhibitor compound effective in the treatment of rheumatoid disorders in dosage amounts not to exceed 900mg per day or until RF or ESR have decreased or returned to normal, and (b) a daily, oral dose in uninterrupted consecutive sequence after cessation of said regimen (a) of a tumor necrosis factor inhibitor compound effective in the treatment of rheumatoid disorders in dosage amounts of less than or more than 100mg/day indefinitely or until RF or ESR stabilize or normalize.

10 The present method of administration of tumor necrosis factor inhibitor such as thalidomide is a significant improvement over the prior art method of treating rheumatoid arthritis published by Gutierrez-Rodriguez. Gutierrez-Rodriguez looked at a narrow range of doses of thalidomide against RA (400-600 mg) for no more than 38 weeks (exclusive of a 300 mg dose for 65 weeks).
15 Gutierrez-Rodriguez also permitted patients to continue taking aspirin or prednisone so that additive or synergistic effects with thalidomide cannot be ruled out.

The following invention teaches the following items which Gutierrez-Rodriguez did not consider.

- 20 1. Treatment doses less than 300 mg or greater than 600 mg.
2. Treatment duration longer than 38 weeks (65 weeks).
3. Elimination of all other drugs (aspirin, steroids) to ensure measure of effectiveness is of thalidomide alone.
4. Maintenance doses less than or more than 100 mg/day.
- 25 5. Maintenance durations longer than 65 weeks.

The methods of the invention include administering to an animal afflicted with a disease arising from an abnormal or undesirable normal immune response (for example, rheumatoid arthritis) an affecting amount of a tumor necrosis factor inhibitor, or a combination of two or more tumor necrosis factor inhibitors, or
30 combinations of tumor necrosis factor inhibitors with anti-inflammatory drugs.

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The animal can further be treated with other disease-modifying anti-rheumatic drugs, cytotoxic drugs, immunosuppressive drugs, and/or steroids. These treatments are to either prevent, ameliorate and/or retard the disease in its progression in the afflicted animal.

- 5 Efficacy in control of symptoms was evaluated by interviewing the patients subjective experiences of the severity of symptoms on a three-graded scale: mild-moderate-severe.

 In another preferred embodiment of the present invention, thalidomide is micronized to a particle size less than 1.0 microns. Thalidomide having this
10 particle size has a much more effective absorption rate than thalidomide of the prior art.

 Another preferred embodiment of the present invention are combinations of tumor necrosis factor inhibitors with non-steroidal anti-inflammatory carboxylic acids. Typical tumor necrosis factor inhibitors which can be used
15 with the present invention include thalidomide, pentoxifylline, and xanthine derivatives.

 The preferred non-steroidal carboxylic acids include the aryl acetic acids, the fenamic acids, the aryl propionic acids, the biphenyl carboxylic acids, and the diphenyl ether carboxylic acids.

- 20 The preferred acetic acids include indomethacin, acetaminophen, cirunetacin, sulindac, tolmetin, zomepirac, diclofenac, fenclofenac, isoxepac, furofenac, fentiazac, clidanac, oxepinac, fenclorac, ionazolac, metiazinice acid, clopirac, amfenac, benzofenac, clometacine, etodolac, bumadizone, and clamidoxic acid.

 The preferred aryl propionic acids include ibuprofen, flurbiprofen,
25 naproxen, ketoprofen, fenoprofen, benoxaprofen, indoprofen, piroprofen, caprofen, oxaprozin, pranoprofen, suprofen, miroprofen, tioxaprofen, alminoprofen, cicloprofen, tiaprofenic acid, furaprofen, butibufen, fenbufen, furobufen, bucloxic acid, and protizinic acid.

 The fenamates acids includes mefenamic acid, flufenamic acid,
30 meclofenamate, niflumic acid, tolfenamic acid, flunixin and clonixin.

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Anti-rheumatic agents which may be used in combination with tumor necrosis factor inhibitors include gold salts such as auriofin and include the penicillamines.

Additional compositions include TNF inhibitors and steroidal anti-inflammatory such as prednisone.

The following are illustrative examples of the present invention.

EXAMPLE I

The following illustrate the micronization of thalidomide. Thalidomide is micronized using a micronizer to a particle size less than one micron, i.e., 0.5 microns.

EXAMPLE II

100mg of thalidomide and 200mg of ibuprofen are mixed. The active ingredients are triturated and Q.S. with lactose to selected capsule size.

EXAMPLE III

15 300mg thalidomide are mixed with 350mg of naproxen. The active ingredients are triturated Q.S. with lactose to selected capsule size.

EXAMPLE IV

500mg thalidomide are mixed with 200mg indomethacin. The active ingredients are triturated Q.S. with lactose to selected capsule size.

EXAMPLE V

Methods of treatment of rheumatoid arthritis.

The following example shows how both compounds and their compositions can be used in treating diseases arising from abnormal or undesirable normal immune responses. Preferably these diseases are autoimmune diseases. More preferably, the autoimmune disease is rheumatoid arthritis. The

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compounds and their compositions can be used to eradicate or reduce the severity of rheumatoid arthritis. Briefly, the afflicted animal is administered an effective amount of thalidomide or a combination of thalidomide with a steroidal or a non-steroidal anti-inflammatory drug or anti-rheumatoid agent. Then both compounds
5 can be administered individually or combined into compositions. The compounds in combinations are hereinafter referred to as compounds. The preferred animal subject is human. The animal can further be treated with disease modifying anti-rheumatic drugs, cytotoxic drugs, immunosuppressive drugs and/or steroids.

The strategy used in treating a particular animal patient depends on his
10 species, age, general health, status of rheumatoid arthritis, etc. For example, the desired dose of compound may be presented as 2,3,4 or more sub-doses administered as infusions or taken orally at appropriate intervals throughout a treatment period. If administered as infusion, administration is by any suitable route such as parenteral (including subcutaneous, intramuscular, intravenous and
15 intradermal). The preferred route is orally in the form of including, but not limited to, tablets or capsules. For example, the patient could take effective doses of thalidomide and ibuprofen tablets or capsules three times a week. It would be appreciated that the preferred route may vary based on the factors discussed above.

20 Additional combination chemotherapy which can be used with tumor necrosis factor inhibitors include compounds such as gold salts, metal chelators, anti-malarials, dapsone, sulfasalazine, and other traditional or new drugs used in the treatment of rheumatoid arthritis. If one of the drugs has side effects, it can be given to patients on alternate treatment periods. Additionally, in combination,
25 the different drugs in the compounds may exert a synergistic effect. Further, the toxicities of the drugs may also be separate and not additive. There can be a trade-off between the toxicity and effectiveness of the drugs.

While the compounds may be administered alone, they may be presented as part of a pharmaceutical formulation. Preferably, compounds are combined
30 with an acceptable carrier. The formulations of this invention may include other

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agents conventional in the art having regard to the type of formulation in question. The formulations can also include other anti-rheumatoid drugs, immunosuppressive drugs and/or steroids. The carrier must be acceptable in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient.

The following is an example of a procedure for administering a formulation containing thalidomide and ibuprofen to a human patient: The patient takes a tablet or capsule containing 300 mg of thalidomide and 100 mg of ibuprofen three times a day. Dosage may be increased by 50 mg of each of the components every two to three weeks. The maximum level of dosage is determined at the point at which unacceptable toxicity first occurs or the patient shows improvement. At the end of the five-day period, the patient is evaluated. The evaluation includes physical examination and extensive laboratory testing. The testing also includes evaluation for toxicity, including somnolence, peripheral neuropathy and constipation. Additional laboratory monitoring includes complete blood cell count every two weeks and then monthly thereafter.

The dosage will be varied by taking into consideration the individual patient's tolerance of the drug, its efficacy and toxicity. Other anti-arthritis drugs mentioned above can be used in combination with the treatments. According to the results of the test, a starting dose of a particular compound is reduced for a patient who exhibits adverse reaction or the drug used in combination with the compounds can be changed or reduced.

The test for monitoring the improvement of the disease can include specific tests-directed, for example, to determination of systemic response to drug(s) which includes erythrocyte sedimentation rate (ESR), articular index (AI), rheumatoid factor (RF) and acute phase reactants (APR) observations are made of the swelling, etc., of the afflicted body parts. Improvement in stiffness, grip and pain of the patient is also observed. If the patient's condition is stable, he is re-treated at the same dosage weekly and evaluated weekly or at lesser dosage(s) if toxicity has occurred. Provided a patient's condition is stable, the

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treatment may be continued. After six months of treatment, anatomical changes of skeleton is determined by radiologic imaging, for example, by x-ray radiography.

At the end of each period, the patient is again evaluated. Comparison of the pre-treatment and post-treatment radiological assessment, ESR, AI, RF and acute phase reactants indicate the efficacy of the treatments. According to the efficacy of the treatments, in the patients condition, the dosages of the components in the formulations may be increased or maintained constant for the duration of treatment.

10 EXAMPLE VI

500 mg of thalidomide and 60 mg of prednisone are mixed. The active ingredients are triturated and as with lactose to selected capsule size.

Although only a few exemplary embodiments of this invention have been described in detail above, those skilled in the art will readily appreciate that many modifications are possible in the exemplary embodiments without materially departing from the novel teachings and advantages of this invention.

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WHAT IS CLAIMED IS:

1. A method for the treatment of rheumatoid disorders which comprises administering to a patient in need of such treatment, a daily dosage form during an uninterrupted consecutive sequence of 365 days, and in
5 accordance with the following regimen: (a) a three time a day, oral dose in an uninterrupted consecutive sequence of not more than 365 days of a tumor necrosis factor inhibitor compound effective in the treatment of rheumatoid disorders in dosage amounts not to exceed 900mg per day or until RF, ESR and/or AI have decreased or returned to normal, and (b) a daily, oral dose in
10 uninterrupted consecutive sequence after cessation of said regimen (a) of a tumor necrosis factor inhibitor compound effective in the treatment of rheumatoid disorders in dosage amounts of between 50mg/week and 100mg/day, indefinitely, or until RF, and/or AI stabilize or normalize.
2. The method of claim 1 wherein said tumor necrosis factor inhibitor
15 compound is selected from the group consisting of thalidomide, pentoxifylline and xanthines.
3. The method of claim 2 wherein said tumor necrosis factor inhibitor compound is thalidomide.
4. The method of claim 1 further including a compound selected from
20 the group consisting of non-steroidal anti-inflammatories, steroidal anti-inflammatories, gold salts, penicillamines or mixtures thereof.
5. A pharmaceutical composition comprising thalidomide and an pharmaceutical acceptable carrier wherein said thalidomide has a particle size of less than one micron.

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6. A pharmaceutical composition comprising: (a) thalidomide; (b) a non-steroidal anti-inflammatory carboxylic acid selected from the group consisting of the aryl acetic acids, the aryl propionic acids, the fenamic acids, the biphenyl carboxylic acids, and the diphenyl ether carboxylic acids; and (c) a pharmaceutical inert carrier.

7. The composition of claim 6 wherein the non-steroidal anti-inflammatory carboxylic acid is an aryl propionic acid.

8. The composition of claim 7 wherein said aryl propionic acid is ibuprofen.

9. The composition of claim 7 wherein said aryl propionic acid is naproxen.

10. The composition of claim 7 wherein said aryl propionic acid is ketoprofen.

11. The composition of claim 7 wherein said aryl propionic acid is fenoprofen.

12. The composition of claim 7 wherein said aryl propionic acid is flurbiprofen.

13. The composition of claim 6 wherein said non-steroidal anti-inflammatory carboxylic acid is an aryl acetic acid.

14. The composition of claim 13 wherein said aryl acetic acid is indomethacin.

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15. The composition of claim 14 wherein said aryl acetic acid is sulindac.

16. A pharmaceutical composition comprising: (a) a tumor necrosis factor inhibitor; (b) a compound selected from the group consisting of (i) non-steroidal anti-inflammatory carboxylic acids; (ii) steroidal anti-inflammatories; (iii) gold salts and (iv) penicillamines; and (c) a non toxic pharmaceutical inert carrier.

17. The compositions of claim 16 wherein said tumor necrosis factor inhibitor is pentoxifylline.

18. The composition of claim 16 wherein said tumor necrosis factor inhibitor is thalidomide and said steroidal anti-inflammatory is a prednisone.

19. The composition of claim 16 wherein said TNF inhibitor is thalidomide and said gold salt is aurofin.

20. The composition of claim 16 wherein said TNF inhibitor is thalidomide and said non-steroidal carboxylic acid is flufenamic acid.

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(54) Title: TREATMENT OF RHEUMATOID ARTHRITIS WITH THALIDOMIDE ALONE OR IN COMBINATION WITH OTHER ANTI-INFLAMMATORY AGENTS		
(57) Abstract The present invention relates to a novel method for treating rheumatoid arthritis with thalidomide alone or in combination with anti-rheumatoid agents and/or with steroidal and/or non-steroidal anti-inflammatory drugs. The present invention also relates to methods of treating rheumatoid arthritis with tumor necrosis factor inhibitors as well as pharmaceutical compositions containing tumor necrosis factor inhibitors and steroidal and/or non-steroidal anti-inflammatory and/or anti-rheumatoid drugs. A further aspect of this invention relates to a special pharmaceutical composition containing thalidomide wherein said thalidomide has been micronized to a particle size of less than 1.0 microns. Compositions containing such micronized thalidomide exhibit faster absorption rates than previously known thalidomide formulations.		

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MAIR J.

INTERNATIONAL SEARCH REPORT

Inter. Patent Application No.

PCT/US 94/08742

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	THE JOURNAL OF RHEUMATOLOGY, vol.16, no.2, 1989 pages 158 - 63 GUTIERREZ-RODRIGUEZ, O. ET AL 'TREATMENT OF REFRACTORY RHEUMATOID ARTHRITIS-THE THALIDOMIDE EXPERIENCE'	1-3
A	see the whole document especially page 158, col.2 line 25 & line 33-34 ---	4,6-16, 18,20
A	WO,A,92 14455 (THE ROCKEFELLER UNIVERSITY) 3 September 1992 see the whole document -----	1-16, 18-20

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 94/08742

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
REMARK: Although claims 1-4 are directed towards a method of treatment of the human/animal body the search has been carried out (for the first subject) and based on the alleged effects of the composition.
2. ☒ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
Claims searchable completely: 1,3,4,5,8-12,14-20
Claims searchable incompletely: 2,6,7,13
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

For further information please see annex.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1,2,4,16 (partially) & 3,5-15,18,19,20

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

CONTINUATION OF BOX II:

Claims 1,2,4,16 (partially) & 3,5-15,18,19,20. Use of pharmaceutical compositions containing Thalidomide alone or in combination with another anti-rheumatoid arthritis agent for the treatment of rheumatoid arthritis.

Claims 1,2,4,16 (partially) & 17. Use of pharmaceutical compositions containing pentoxifylline and xanthines alone or in combination with another anti-rheumatoid arthritis agent for the treatment of rheumatoid arthritis.

information on patent family members

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Form PCT/ISA/210 (patent family annex) (July 1992)